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Report from The Meeting: "Open Source Software Framework for Organ Modeling & Simulation"

G. Higgins and H. Kelly

Researchers met at the National Library of Medicine on July 23-24, 2001 to brainstorm about the next stage in the development of a "Digital Human". This meeting, called "Open Source Software Framework for Organ Modeling & Simulation", was organized to review the current state of computer-based modeling in medicine, identify critical "next steps" for technical resource development, and create a vision for building useful and functional computer models of human biology. The long term vision is the development of accurate and validated models and simulations of cells, tissues, organs and organ systems that can serve as frameworks for experimental analysis, patient care, and training in biology and medicine.

Web resources:

Digital Human web site, resources: www.fas.org/dh
Digital Human web site, collaborative software development: hq.fas.org/digitalhuman

PROPOSAL

The Digital Human Consortium

A. Why a Digital Human?

The Digital Human consortium will use 21st century information technology tools to simulate the functions of genes and proteins, cells, tissues, organs, and gross a key role in helping biomedical researchers master the staggering complexity of their discoveries and help physicians make effective use of their discoveries to improve health, and help engineers imitate biological mechanisms to achieve revolutionary change in computing and chemical manufacture, and the design of artificial organs, robots, and a variety of other areas. While this ambitious goal will clearly not be quickly or easily achieved, near-term progress in many areas can benefit from having a shared framework in which researchers can combine their resullts.Clearly it must be the work of many hands.The Digital Human will contribute by (1) providing a community that will allow researchers, medical personnel, and engineers to share their work, build on each other's efforts, and (2) allow biomedical researchers and computer scientists to work effectively together to develop a language that will allow this to happen. The process will allow many creative developers to re-use and build on each other's work. While nothing on

the scale of the Digital Human has been attempted before, the Open Software experience provides a valid model that can be built upon.

(a) Information Technologies Have Become Essential

Living systems and the human body in particular, are the most complex systems known. A deep understanding of how they function will give us unprecedented power to improve health. Mimicking biological systems will give us an extraordinary set of new tools that could increase economic productivity while reducing pollution and our need for natural resources.

But unlike other areas of science, our understanding of biological systems cannot be reduced to insights captured in a few equations. As we probe deeper, the systems appear ever more intricate, more diverse, and more astonishing. Understanding these systems, therefore, requires both an enormous number of detailed experiments and finding a way to tie this information together and make sense out if it. The explosion of information available from sequencing entire genomes and growing sophistication in many other fields means that simple models of behavior are being replaced with more complex, more realistic models involving the interaction of hundreds of phenomena. Few important phenomena are likely to be explained by a "one-gene theory", for example. Most disease states can be understood only by following the interaction of thousands of different genes working in complex networks.

The complexity of this analysis has grown to the point where biological systems can only be understood by using modern computers. Computers were essential for sequencing the human genome and will be even more important in understanding how the genome works by developing computer simulations of their functions. These tools can also make it easier to visualize the operation of complex systems – how cells assemble the miniature machines they need or how defects in electrical networks degrade the performance of a heart – and see what may happens by intervening with new drugs, surgeries, or other therapies.

(b) Inventing a New Model for Collaboration

But building the software needed to describe the dynamic operation of cells and organs requires developing a new way of representing the research results. Just as the definitions of how to represent information on the Internet led to the growth of the World Wide Web, the Digital Human project will develop a language allowing research teams to combine their results and build simulations capable of addressing complex, practical problems.

Such simulations have already proven themselves capable of producing useful results. Computer modeling provides crucial help for biomedical research, the design of artificial hips and organs, anticipate the effects of crash tests, design

robots, and create animated humans for games and movies. Much more can be achieved in the next few years.

Progress will, however, be much faster if the diverse community now developing simulations is able to work together efficiently and developers can save time by building on each other's work. But without an effective community, and a common vocabulary, most of these projects must start from scratch. Simulations can and must be built with out the Digital Human Consortium. But an effective community will make the process faster, reduce duplication of effort and costs, and reduce bugs and errors. The community would ensure that diverse groups benefit from each other's work, and from the testing and bug reporting that would result from widespread use and testing. The core mission of the Digital Human Consortium is helping such a community to form and operate effectively.

The ***Digital Human Consortium*** will provide a forum and a framework to develop models and simulations that can interoperate for larger scale modeling of complex systems such as gene regulatory networks and multi-level organ systems. The consortium will ensure that the models and simulations are valid and accurate, and it will provide a framework allowing interoperation and reuse of models and simulations that developed by a diverse research community. The work must combine many disciplines including computer science, cell biology, molecular biology, physiology, pathology, pharmacology and anatomy.

There should be no illusions about the difficulty of this task. The consortium recognizes the need to advance incrementally but the virtue of doing so within the framework of a broad reference model. While useful products can be expected from the tools developed by the Digital Human Consortium during the next few years, we may never have a complete understanding of human systems. Countless discoveries are needed in biology and medicine and new information tools must be developed. But now is the time to begin.

B. The Utility of Biological Simulation

Biological simulations are being built for a wide range of purposes including medical research, education and training, medical practice, robotics and biomimetics, and human factors simulations. All would benefit from a shared set of valid simulation tools that would prevent duplication of effort – letting each group spend more time on solving the problems that interest them most instead of working on software. Here are some examples.

(a) Biomedical Research

Modeling and simulation has been used for years in biomedical science as an adjunct to experimental work performed in "wet lab" experiments. Data gathered from *in vitro* and *in vivo* studies can be analyzed *in silico* and combined with insights from many other experiments to generate new hypotheses that can be tested in the laboratory. Most computer models and simulations have been

developed in isolation and few attempts have been made to share computational strategies and data outside of conventional publication channels.

Recently, several communities of researchers and clinicians have realized the benefits of working in consortia working on models that span multiple levels of biological organization, integrating anatomy, physiology, biomechanics, cell biology and biochemistry. These include integrated models of the vertical organization of some of the major organs (heart, lung, muscle) as well as horizontally-integrated models of major physiological systems (circulatory, respiratory, immune). Visualization and simulation technology may soon allow users to move seamlessly between different spatial resolutions (molecular to organ level) and different temporal states (development through aging; varying physiologic state) within an integrated simulation.

Simulations of the Heart

Investigators working in cardiac modeling and simulation provide a particularly compelling example. Sophisticated models of cellular, tissue and organ systems have been built from a variety of data sources: diagnostic images, electrophysiological measures, biomechanics, bioelectric fields and ionic studies. The teams have used this model to build sophisticated simulations that provide insight into the physiology of the heart not possible from studies limited to a single level of analysis. The models have, for example, allowed a detailed understanding of the mechanisms of heart disease, such as arrthymias, ischemia and myopathy that allow them to explore a range of potential new strategies for therapies. Clancy and Rudy (1999), for example, showed that a mutation in the SCN5A gene produces a structurally defective sodium channel that causes cardiac arrhythmia when inserted into an integrated, quantitative computer model of a cardiac cell.

Modeling the Molecular Biology of the Cell

A significant application this strategy will be development of a context in which to understand the function of new gene products derived from the human genome project, genes can be screened for normal and abnormal function (so-called "phenotype screening") using validated computer models and simulations of cells and organs. Thus, a candidate gene product whose function is unknown can be inserted into the requisite computational model, and the consequences of its expression can be studied within these higher order simulations.

Success in sequencing the human genome, as well as the sequencing of many other animal and plant species, has greatly accelerated research to understand the complex functions of individual genes, and the way the expression of one gene can affect the actions of others. Understanding these operations requires understanding complex sequences of operations that are in many ways analogous to complex electric circuits. Several genes may need to be expressed, and several others suppressed, for a biological function to occur.

Simulations allow researchers to assemble information that has been gathered about the functions of many different genes, and their reaction to their environments, and understand how networks of hundreds of genes operate together. These simulations allow experimental biologists to make conjectures about the responses of complex biological processes in a simulated environment, without having to conduct studies *in vitro*, on animals, or in human patients. These predictions, of course, eventually need to be validated *in vivo*. But the models provide a powerful tool to help point *in vivo* research in the most promising directions.

For example, predictive models of generic cell types such as red blood cells, eukaryocytes and prokaryocytes could be used to screen the effects of novel drugs in pharmacological research, identifying candidate drugs that show efficacy on simulated receptors in simulated cells. Similarly, patient-specific organ models could be developed from diagnostic images and physiologic data and used to predict the effect of novel pathogens on the individual tissues of a particular patient. Von Dassow et al (1999) showed the value of predictive modeling in biology, when their *simulated* Drosophila embryo was able to generate accurate patterns of developmental segmentation, based solely on the activity of 136 coupled equations with 50 parameters for the processing of gene products.

(b) Clinical Practice

Accurate computer models can play a key role in developing new medical procedures, helping physicians plan radiation therapies, design prosthetics and artificial organs, and communicate with patients and other health providers.

Interventional Planning

The computer models built by members of the Digital Human Consortium will provide reference standard for image analysis, anatomical landmarking, pathological classification, image-guidance for therapies and procedures, and patient comparison. The generic models can be extended to represent models of individual patients by using information from a variety of new imaging devices (MRI, CAT, PET). These simulations can, for example, combine new imaging modalities and the development of computer-based diagnostic systems for detection of tumors and other lesions. These models can allow surgical teams to plan procedures on accurate models of an actual patient's condition and aid therapists planning to target tumors with specific doses of radiation or chemicals. The models could greatly reduce risks and errors.

In the long run, Digital Human simulations can speed the development of new drugs and therapies. Accurate models would let physicians explore the impact of different therapies on the specific pathology and disease condition of an individual to be displayed and customized for very individualized therapies. These may include heart surgeries, customized drug interventions, and tumor and cancer resections, with full knowledge of the exact spread of the problem and the margins of safe and effective therapy.

Artificial Organs and Prosthetics

Computer models are already being used to design artificial hips, hearing aids, prosthetics and other devices fitted precisely to the requirements of individual patients. The Digital Human will provide a reference model that would increase the accuracy and validity of these designs, as well as speeding the development of a much wider variety of devices. By combining a vast amount of measured information into a single model, the Digital Human simulations would provide a powerful tool for learning how to mimic the operation of human organs – whether the heart, or kidneys, or the ear. They would also help ensure an accurate interface between artificial organs and the environment in which they will function (including their performance under extreme conditions that would be otherwise difficult to test).

A New Kind of Medical Record

'Body-double', patient-specific image models can be created to serve as a repository for diagnostic, pathologic and other medical information about a patient. These will serve as a three-dimensional (3-D) template for enhancing communication between patient and physician, and provide a reference framework to examine pathologic and age-related changes that occur over time.

(c) Medical Training and Education

Computer simulations are becoming critical for extracting meaning from the complex information emerging from biological research. It is also becoming critical for students to learn this material for the first time, and to help experts keep pace with discovery. Much of the information about biological operations can be made much more vivid, and understandable, if it is shown visually. Text and two dimensional drawings in texts and journals can not convey information as forcefully as a simulation that allows a student to see the full dimensions of something like a heart, see how the components operate, and understand the impact of different diseases and clinical interventions. This is just as true understanding operations at the microscopic level of a cell where operations of organelles, cell walls, self-assembled motor structures can be simulated and visualized in compelling ways. Simulations allow students to explore and practice in ways that do no harm. And they make it possible for students to understand the diversity of biological systems helping prepare them to expect the unexpected.

Medical Schools

Medical schools are finding it increasingly difficult to attract new instructors willing to teach introductory courses – particularly human anatomy. Departments of Anatomy are being abolished or incorporated into other departments. The generation of basic science faculty adept at teaching gross anatomy is dying out. Graduate programs in anatomy no longer require training and teaching, but rather emphasize research in neurobiology, molecular biology and cell biology.

While the simulations made possible by the Digital Human consortium can obviously not provide a comprehensive solution, they could provide crucial new tools. Powerful simulations can let students learn more about the structure and function of anatomy than traditional techniques. The new tools would permit a new kind of pedagogy – based on exploration and apprenticeship – much more powerful than conventional work with texts and the occasional cadaver. The simulations could capture the expertise of existing teachers and give new teachers room to invent new tools and new approaches to instruction built around state-of-the-art models of human function captured in simulations built for research purposes.

Achieving this kind of instruction, of course, would require a unique collaboration beteen computer scientists, cognitive scientists, anatomists, physiologists to develop a new generation of models, simulations, educational programs that can support true user interaction with simulated human organs, including validated physical and physiological properties, such as real-time tissue deformability, realistic bleeding and accurate haptics ("touch and feel"). These simulators will support high bandwidth access will facilitate distributed visualization and simulation of models for medical education and research and development applications.

Continuing Education for Surgeons and Other Medical Specialists

One immediate benefit of an integrated Digital Human will be to provide simulators for practicing difficult procedures for medical professionals at all levels.

There is a growing public awareness that physicians and other healthcare workers make mistakes. Many of these mistakes are purely technical in nature; sometimes these errors are fatal. Recent studies suggest that up to 100,000 Americans die every year from medical errors. The future trend is toward even greater liability risks, regulatory oversight, and higher entry-level skills. Repeated certification and skill demonstration is now obligatory. Complex surgical procedures such as hip replacement, skull base surgery, complex liver surgery, can be rehearsed in the virtual environment using the patient's anatomy prior to the actual procedure, and health practitioners can be certified using accurate models and simulations based on the Digital Human. Medical schools are struggling to remain solvent. Academic medical centers are urgently seeking cost-effective solutions to expensive training and residency programs. Thousands of medical personnel throughout the world need to train and practice invasive procedures. The cost of using operating room time for training surgical residents has been estimated at $53 million in the United States alone. Opportunities to learn and practice these vital skills on animals and humans diminish as public expectations rise at the same time as hospitalizations and length of stay decrease.

Computer-based medical simulation can be used to train healthcare providers in a spectrum of medical skills from planning and diagnostics, through minimally

invasive procedures, up to the most complex, high-risk procedures. The advent of high performance computing on the desktop, coupled with the enhanced realism of computer graphics models of the human body, makes this technology available now for *safe and effective* training. Simulation can be used to bridge the information gap between patient and textbook and between practitioners and patient for patient education.

(d) Biomimetics and Robotics

Biological systems perform extraordinary feats that could open revolutionary new dimensions in computing, data storage, environmentally benign chemical manufacturing, and many other areas. Robot designers continue to struggle to imitate aspects of locomotion, cognition, and navigation mastered by the most primitive animals. These efforts could be greatly assisted by Digital Human simulations that provided powerful explanations of the operation of real biological systems.

(e) Human Factors

Many engineering designs are based on models of their impact on humans humans can operate safely and effectively. These can range from the design of vehicle seats and parachute harnesses to the design of safe cockpits and automobiles. Accurate simulations could predict the impact of a wide variety of extreme events on the human body. Combined with mechanical simulations of vehicles, the digital human simulations could predict the impact of a variety of extreme events on the human body (side collisions, rapid acceleration). They could even anticipate the impact of phenomena that can not be measured directly.. such as the impact of prolonged weightlessness in a long-duration NASA mission and the effectiveness of different interventions.

C. What Must Happen to Build the Digital Human Consortium

The Digital Human Consortium would build simulations capable of achieving these ambitious goals by providing a forum where a diverse group of developers can share, test, and build on each other's work. Researchers would be able to express new insights into the role of a specific gene in a language that would permit easy integration with other work. Drug designers, clinicians, teachers, human factors experts and others would be able to draw on validated, up-to-date simulations build by others and apply their creative energies to using the tools to achieve specific goals. Under current circumstances, each group builds redundant models.

But getting to a point where many groups can contribute to, and share in the Digital Human model, requires (1) building a community that could define the technical, legal, and other aspects of sharing, and (2) designing specific technical

tools for ensuring interoperability of components (tools that define the interface between components, for example, and represent the geometry of objects in ways that permit a viewer to represent the combined operation of all components.) Building an Open Source Community

The Digital Human is a software consortium that is building a collaborative approach for the design and development of biomedical simulations and models. In this scenario, developers of a heart model would be able to plug their software into another group's lung model, and these models could interact in a meaningful and accurate simulation of actual cardiovascular-respiratory interaction. Similarly, software components modeled after molecules, cells and tissues could be integrated in a hierarchy to produce a valid representation of a functional organ such as a heart or liver. To achieve this goal, it is critical that developers engage in a collaborative software development process in which biomedical models and simulations are verified and validated by the larger biomedical research community.

(a) Building the Community

There's no hiding from the daunting difficulty of improving communication among of the diverse, creative individuals and groups working in areas related to biological simulation. While funding agencies can encourage participation, in the long-run the Digital Human consortium will succeed only if it presents unambiguous benefits to the participants and if the transaction costs of participation – primarily the investment of precious time – are low. The minimum goals of a successful community are:

- A process for developing a technical architecture permitting the widest possible collaboration and sharing/reuse of components.
- Simple, clear rules for managing intellectual property
- Efficient procedures for peer-review and testing, bug reports, issue tracking software/biological validation, and procedures for releasing approved versions
- Easy procedures for version control, managing continuous build test revise cycles
- Clear identification of authors, sources of data and methods (both to trace and correct problems and to ensure adequate credit is given to creators)
- Ease in building business around extensions and services

The experience gained by the Open Software community provides a valuable model. The Mozilla process, for example, has resulted in successful projects even in projects involving millions of lines of code and a thousand developers.[1] It

[1] Frank Hecker, "Lessons from Open Source Software Development:The Mozilla Experience", Proceedings of the Open Source Software Framework for Organ Modeling and Simulation Conference July 23-24, 2001

proves that given the right incentives, a diverse group of developers can maintain their independence and creativity while gaining enormous efficiencies by sharing each other's work. New information tools can greatly facilitate the process by making it easier to share work and conversations online and providing semi-automated checks of technical validty.

Few simulation projects in biomedical research benefit from sharing interoperable software components. In most cases individual researchers are managed as stand-alone, "stove-pipe", projects. But there is a growing sense that the complexity of the task has made this style of operation increasingly inefficient and frustrating for the participants.

In the Digital Human Consortium there will be stringent requirements not just for technical validity of the code but strict peer review and evaluation to ensure that the underlying biological models are valid. Careful procedures to verify the sources and accuracy of data used to build biomedical models and simulations are essential if the tools are ever to be adopted as a legitimate platform for experimentation and clinical practice. But if the open consortium operates as hoped, the number of reviewers and valuators can be very large, and the process of review and improvement can be continuous.

D. Our Proposal

We propose to build a management process for the Digital Human Consortium that will roughly follow the successful model of large-scale open source projects. Ideally the funding agencies would be comprised of the following elements:

- Senior officials from public agencies (and possibly companies) funding major portions of the code development would constitute a policy making board of directors.
- A Steering Committee would be appointed to manage the day to day operation of the project, including managing the required collaborative web-sites and data-bases. These people would work nearly full time on the project, would *facilitate* (and importantly not *direct*) the process, gaining consensus on policies and procedures, making "tie-breaking decisions" when disputes arise, and ensuring consistency among the projects.[2]
- Individual development efforts would be organized by "Project Leads" (also known as "component owners" or "module-owners") having primary responsibility for a given component (e.g., "liver", "user interface tools", etc).

The Project Lead would typically work with a handful of other developers (say, 5-9 individuals); the Project Lead and his or her associated developers would together be the primary individuals responsible for creating the code and related material associated with their component. (Although other individuals may

[2] We propose that the following individuals serve as initial members of this group: Adam Arkin, Brian Athey, Jim Bassingthwaighte, Parvati Dev, Tom Garvey, Frank Hecker, Gerry Higgins, Chris Johnson, Henry Kelly, Bill Lorensen, Andrew McCulloch, Ken Salisbury, Shankar Sastry

contribute code for use with the component, based on experience in open source projects the Project Lead and associated developers will likely produce 90% or more of the code and other material associated with the component.) Project Leads would have permission to enter and change code in the official version of the Digital Human; they may also approve such access for other individuals, including developers on their own teams.

In addition to being responsible for the technical development of their own modules, Project Leads would also be responsible for coordinating with the Project Leads for other modules, to ensure that the work performed by their team is coordinated with work performed by other teams. An overall Architecture Committee (or Technical Coordination Board), consisting of the Project Leads from all of the components of the project (or a representative subset thereof), would be responsible for overall technical decisions related to development activities for the Digital Human.

The small teams responsible for the various components would encourage collaboration and participation from a much larger group of people who would contribute components and review the work. This larger group would include several hundred individuals from academic, government, or industry research groups and would not necessarily be associated with any of the funding agencies. The members of the team would be authorized to work with pre-release versions of the Digital Human code, design documents, bug reports, and other project material, but would not have permission to change the official version of the Digital Human project code and data.

(b) Technical Architecture

A key element of the Digital Human project will be to ensure that software components developed by different developers will work efficiently together. This means, for example, that a functioning heart model could be assembled by combining simulations of valves and other heart components built by different groups – and those individual components are easy to replace. A valve modeling the characteristics of a particular individual could, for example, be substituted for a generic valve.

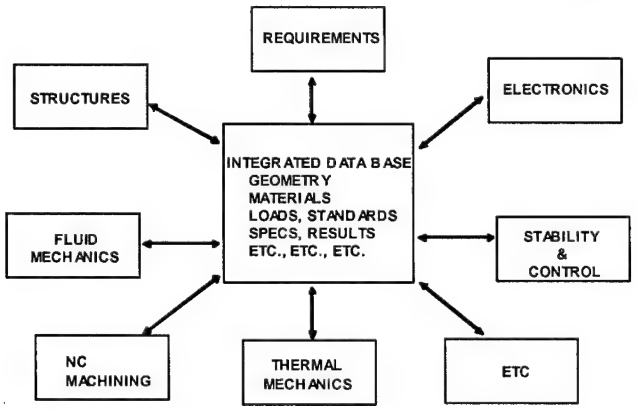
An effective technical architecture would:

- Encourage creative, competing solution
- Adaptable to new concepts and discovery and accommodate existing models and simulations, while providing guidance for models yet to be developed.
- Not tied to a specific platform or programming language
- Highest possible compatibility with existing models.

- Rooted in biology (principles of biological organization, structured by natural representations of ontology and object interaction)-- no forced programming artifacts
- Minimize bureaucratic and computational overhead
- Accommodate both vertical components (e.g., modules at organ, tissue, cell levels) and horizontal components (e.g., user interface, security).

The engineering community has developed sophisticated approaches for developing technical architectures. The STEP standard[3], for example, provides a way to create drawings and simulations of complex aircraft and other systems that may involve thousands of components and hundreds of different designers. While the details of the way these systems manage geometry, pass information about fluid flows, and other aspects of visualization and simulation will differ, the experience these groups have had in developing functioning, interoperable components will be examined closely.

COMPUTER BASED ENGINEERING SYSTEMS



Over the long term, a large number of projects (under the "project leads" described above) will need to be developed. Topics will include

- Developing a unified ontology that would permit clear identification of components from gross anatomy to molecular components of cells
- Defining geometry so that components fit together properly and provide a precise basis for modeling physical connections and material flows.
- Defining models of physical motion and deformation
- Defining signal flows (chemical, electrical)
- Defining material flows
- Defining chemical transformations (including gene expression)
- User interface tools (including visualization, tools for building circuits of gene expression, etc.)
- Applications (teaching tools, research tools, human factors models)

[3] Robert Fulton, An Overview of Computer Aided Systems Design/Engineering Systems and Data, Proceedings of the Open Source Software Framework for Organ Modeling and Simulation Conference July 23-24, 2001

Undoubtedly many more topics, and subtopics, will need to be introduced over time. Since it will not be feasible to undertake a complete set of these tasks at the beginning, we propose that the Digital Human project begin with four projects: (1) a unified ontology, (2) Defining a geometry model, (3) Building gene expression networks, and (4) Building post-secondary teaching tools.

(1) Unified Ontology

Ontology is an explicit specification of a conceptualization. For the Digital Human, it is necessary to define the objects and relationships that represent all of the molecular, cellular, tissue, organ and system objects. This set of objects, and the describable relationships among them, are reflected in the representational vocabulary with which a knowledge-based software program represents knowledge. Thus, we can describe the ontology of a program by defining a set of representational terms. In such an ontology, definitions associate the names of entities in the universe of discourse (e.g., classes, relations, functions, or other objects) with human-readable text describing what the names mean, and formal axioms that constrain the interpretation and well-formed use of these terms. Most biological simulation models are founded on a sharply defined ontology, which allows a terse mapping of biology onto computer architecture. This is an important source of the power of such models.

A great deal of effort has been focused on the development of ontology in biology. For example, the Gene Ontology Consortium develops knowledge representation for eukaryotic cells (see http://www.geneontology.org/). Another example is the Bionome project, (http://www.ibc.wustl.edu/moirai/moirai.html) which models biochemical reactions and pathways that are representations as interactions of concentrations, without spatial distribution except as separated into compartments.
In contrast to these efforts, the Digital Human needs to develop an ontology that can unify both higher-level organ models and lower-level molecular and cellular models. As a first task, it is suggested that the Digital Anatomist Foundational Model of Rosse et al .
(1998;http://www1.biostr.washington.edu/~onard/AMIApapers/D005094.pdf), which specifies higher order structures and their relationships, with the emerging BioSPOICE ontology being developed by Garvey, Lincoln and Arkin.

While most work in ontology has focused on providing precise descriptions of objects such as organs, tissues, and cells, it will also be important to build systematic descriptions of the processes and actions of these components. The Biospice project, for example, will define chemical flows and transformations in cells. An analogous non-spatial ontology is typical for whole-body metabolic models such as QCP (http://www.biosim.com/: named for "quantitative circulatory physiology"), which specifies interactions between certain endocrine concentrations, blood pressure, etc., and simulates interventions like

hemodialysis, change in diet, change in environment, various pumps, drips, stimulators and pharmacological agonists and antagonists. The system quantifies the homeostatic actions of many organ-systems, but it only names some chemicals in the chains: it contains no anatomical maps. Similarly, the Cardiome seeks to "Integrate biophysical models of the cardiac action potential, excitation-contraction coupling, and cross-bridge cycling into tissue and organ-level models and develop a unified, Web-based interface to these cellular models that can serve as a common entry point to a database of model parameters", requiring what a model 'is' to be pre-defined. This aims at a tightly integrated structure for the collective model, where the internal structure of a part follows as standard pattern.

Proposed Ontology Team: Tom Colatsky, Tom Garvey, Gerry Higgins, Henry Kelly, Cornelius Rosse.

(2) *Geometry*

Biological objects, such as cells, tissues, organs and organisms have some geometric features that are difficult to model in a realistic manner using conventional engineering methods. Since modeling involves simplification, engineering approaches such as STEP may provide a useful framework for static and certain dynamic models of organs and their relationships. More complicated behaviors such as deformation may be modeled using well-understood, physics-based models.

A fundamental property of the Digital Human will be to coordinate spatial interactions between different models and simulations. A reasonable, highest-common-factor geometrical communication standard for surfaces (membranes or volume boundaries) is the triangulated mesh, specifying at least (x,y,z) positions for vertices and listing triples of vertex IDs to give triangles that will move with them. All other geometrical descriptors can be used to generate such a mesh, with variable levels of detail. While it is hard for a model whose internal description scheme is a NURBS (Non-uniform Rational B-Spline) patchwork to generate one automatically from mesh data, it should be able to handle collision with an object whose shape is specified this way, and accept and use its transfer messages. Other surface descriptors with significant usage in the Digital Human community should have standards by which a model may communicate them, but an agreed mesh format is basic, and should be defined early on in the process.

Similarly, every model involving a deformable volume should be able to export information about it in terms of a mesh of tetrahedra, the natural solid generalization of triangles. Many other primitives are possible, but all can be 'factorized' into tetrahedra, while few can be exactly re-expressed in terms of others. In general, inclusion of formats should come from consensus rather than an isolated committee's preference for some form with advantages for particular modeling purposes.

The language for curves (center lines of blood vessels, *etc.*) must clearly include 3D networks with straight segments between vertices. Some more curvilinear formats are in wide use, such as piecewise cubic polynomial curves fitted together as B-splines – which of these formats to include in a first version of the Digital Human standard is a matter for discussion.

Proposed Geometry Team: Bill Lorensen, Dmitris Metaxas, Tim Poston, Andrzej Przekwas.

(2) Anatomy Training and Surgical Simulation

The first application team to be formed will focus on Anatomy training, as this has been identified as a priority by the meeting's participants. The absence of qualified teachers in anatomy coupled with the obsolescence of the medical school basic science curriculum, suggests that this is one of the most important application priorities that could be targeted by the Digital Human Consortium.

Anatomy Training: Brian Athey, Parvati Dev, Gerry Higgins, Marsha Jessup, Don Jenkins, Henry Kelly.

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